

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



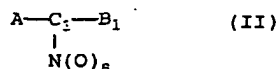
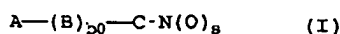
(43) International Publication Date
19 October 2000 (19.10.2000)

PCT

(10) International Publication Number
WO 00/61604 A3

- (51) International Patent Classification⁷: C07J 41/00, A61K 31/575
- (21) International Application Number: PCT/EP00/03238
- (22) International Filing Date: 11 April 2000 (11.04.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
MI99A000751 13 April 1999 (13.04.1999) IT
- (71) Applicant (for all designated States except US): NICOX S.A. [FR/FR]; 45, avenue Kléber, F-75116 Paris (FR).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): DEL SOLDATO, Piero [IT/IT]; Via Toti, 22, I-20052 Monza (IT).
- (74) Agents: SAMA, Daniele et al.; Sama Patents, Via G.B. Morgagni, 2, I-20129 Milano (IT).
- (81) Designated States (*national*): AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, DM, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— With international search report.
- (88) Date of publication of the international search report:
15 March 2001
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHARMACEUTICAL COMPOUNDS



(57) Abstract: Steroidal compounds or their salts having general formulas (I) and (II) wherein: s is an integer equal to 1 or 2, preferably s = 2; b0 = 0 or 1; A = R-, wherein R is the steroidal drug radical, C and C₁ are two bivalent radicals. The precursors of the radicals B and B₁ are such as to meet the pharmacological tests reported in the description.

WO 00/61604 A3

INTERNATIONAL SEARCH REPORT

Internal Application No

PCT/EP 00/03238

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07J41/00 A61K31/575

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| Y | WO 98 15568 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 16 April 1998 (1998-04-16) page 23, table examples 1,3 | 1,2,4, 7-12 |
| Y | WO 97 41144 A (SEARLE & CO ;TJOENG FOE S (US); CURRIE MARK G (US); ZUPEC MARK E () 6 November 1997 (1997-11-06) page 38, table page 4, paragraph 2; examples 21-26 | 1,2,4, 7-12 |
| A | WO 97 21721 A (SEARLE & CO ;TJOENG FOE S (US); CURRIE MARK G (US); ZUPEC MARK E () 19 June 1997 (1997-06-19) the whole document | 1,2,4, 7-12 |
| | -/-- | |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

21 November 2000

Date of mailing of the international search report

20.12.2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Watchorn, P

INTERNATIONAL SEARCH REPORT

Internat. Appl. No.

PCT/EP 00/03238

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| Y | EP 0 436 936 A (HOECHST AG) 17 July 1991 (1991-07-17) page 2, line 11 - line 12; examples 1,2,42,43 --- | 1,2,4, 7-12 |
| Y | EP 0 290 885 A (CHIESI FARMA SPA) 17 November 1988 (1988-11-17) page 3, line 12 - line 15 table I, compound IV; table II, compound VII; table III, compounds IV and VII --- | 1,2,4, 7-12 |
| Y | CEDERQVIST B ET AL: "DIRECT DEMONSTRATION OF NO FORMATION IN VIVO FROM ORGANIC NITRITES AND NITRATES, AND CORRELATION TO EFFECTS ON BLOOD PRESSURE AND TO IN VITRO EFFECTS" BIOCHEMICAL PHARMACOLOGY, GB, PERGAMON, OXFORD, vol. 47, no. 6, 1994, pages 1047-1053, XP000671053 ISSN: 0006-2952 page 1047, column 1, paragraph 2 -column 2, paragraph 1 --- | 1,2,4, 7-12 |
| Y | PATENT ABSTRACTS OF JAPAN vol. 007, no. 131 (C-169), 8 June 1983 (1983-06-08) & JP 58 045724 A (ORIZA YUKA KK), 17 March 1983 (1983-03-17) abstract --- | 1,2,4, 7-12 |
| Y | DE 196 34 793 A (SANOL ARZNEI SCHWARZ GMBH) 5 March 1998 (1998-03-05) page 2, line 2 - line 20; examples 1-3,5,7,8 --- | 1,2,4, 7-12 |
| Y | WO 88 00202 A (UNIV LOUIS PASTEUR DE STRASBOU) 14 January 1988 (1988-01-14) page 6, paragraphs 3,5 page 9, line 5 - line 9 --- | 1,2,4, 7-12 |
| Y | US 3 702 335 A (LAFILLE CLAUDE) 7 November 1972 (1972-11-07) column 10, paragraph 1; example 10 --- | 1,2,4, 7-12 |
| Y | CHEMICAL ABSTRACTS, vol. 118, no. 17, 26 April 1993 (1993-04-26) Columbus, Ohio, US; abstract no. 169434, HORI, KIMIHIKO ET AL: "21-Substituted steroids" XP002153479 abstract & JP 04 273892 A (KAO CORP., JAPAN) 30 September 1992 (1992-09-30) --- | 1,2,4, 7-12 |
| | -/-- | |

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/03238

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-------------------------|
| Y | <p>CHEMICAL ABSTRACTS, vol. 130, no. 21, 24 May 1999 (1999-05-24) Columbus, Ohio, US; abstract no. 276039, BONN, R. ET AL: "SP/W-5186: a novel sulfhydryl-containing NO donor" XP002153480 abstract & CARDIOVASC. DRUG REV. (1998), 16(3), 195-211 ,</p> <p style="text-align: center;">-----</p> | <p>1,2,4, 7-12</p> |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/03238

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1,2,4,7-12 (partially searched) 3,5,6 (not searched)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,
no additional fees are to be refunded.

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☒ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,2,4,7-12 (partially searched) 3,5,6 (not searched)

Please note that the subject matter searched in the context of the present application is limited both under according to Art.17(2)(a)(ii) PCT (for the reasons given below) and according to Art.17(3)(a) PCT (due to a lack of unity the reasons for which are given separately).

Present claims 1-12 relate to an extremely large number of possible compounds and pharmaceutical compositions and uses thereof. In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

Furthermore, present claims 1-12 relate to compounds defined by reference to a desirable characteristic or property, namely the compounds are defined such that they attain a certain level of anti-oxidative activity evidenced according to test 4 or test 5 (both of which are elucidated in claim 1). Since this property (anti-oxidative activity) is in fact the problem to be solved by the compounds of the present application (see page 6, lines 2-7 of the description) - this means that the claimed compounds are defined in terms of their being a solution to this problem. It does not matter that there is also a generic Markush structural formula giving some degree of structural definition to the claimed compounds because the scope of this structural definition is extremely broad in terms of structural features (see above) the restriction of this very broad set of compounds by means of the desideratum is effectively the allegedly characterising feature of the claims (in particular independent compound claim 1) and so the technical meaning of this desideratum is essential in establishing the true scope of the claim according to Art.6 PCT. Since the skilled person is given no idea as to how to limit the broad scope of the compounds of claim 1 (and the uses and compositions thereof according to claims 10-12) to compounds which actually solve this problem, he must by necessity employ an inventive step according to Art.33(3) PCT in order to move from the disclosure of the claimed invention as given in claim 1 (and the uses and compositions thereof according to claims 10-12) to a viable product which actually solves this problem. Consequently the compounds of claim 1 are insufficiently disclosed according to Art.5 PCT to such an extent that no meaningful search is possible based on the full scope of claim 1.

Furthermore, the claims cover all compounds (claim 1) and uses and compositions (claims 10-12) having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds (and their uses and compositions). In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the specific compounds of the examples and their uses and compositions thereof.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,2,4,7-12 (in part)

Compounds of examples 1 and 2 - being the 3-(4-nitrooxy)-nbutyl ester of ursodeoxycholy-ferulate and chenodesoxycholy-ferulate respectively, their uses in the preparation of medicaments and compositions and pharmaceutical formulations containing them.

2. Claims: 1,2,4,7-12 (in part)

Compounds of examples 3-5 being:-

Example 3

(11.beta.)

11,17-Dihydroxy-21-'N-acetyl-S-(4-nitroxybutyroyl)cysteinyloxy!-pregna-1,4-diene-3,20-dione

Example 4

(11.beta.)

11,17-Dihydroxy-21-'N-acetyl-S-(4-nitroxybutyroyl)cysteinyloxy!-pregna-4-ene-3,20-dione

Example 5

(11.beta., 16.alpha.)

9-Fluoro-11,17-dihydroxy-21-'N-acetyl-S-(4-nitroxybutyroyl)cysteinyloxy!-16-methylpregna-1,4-dien-3,20-dione

, their uses in the preparation of medicaments and compositions and pharmaceutical formulations containing them.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/03238

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|----------------------------|---------------------|
| WO 9815568 | A | 16-04-1998 | IT MI962048 A | 06-04-1998 |
| | | | AU 719250 B | 04-05-2000 |
| | | | AU 4780397 A | 05-05-1998 |
| | | | BR 9711586 A | 24-08-1999 |
| | | | CN 1253563 A | 17-05-2000 |
| | | | EP 0929565 A | 21-07-1999 |
| | | | HU 9904149 A | 28-04-2000 |
| WO 9741144 | A | 06-11-1997 | US 5837698 A | 17-11-1998 |
| | | | AU 2922797 A | 19-11-1997 |
| | | | EP 0900233 A | 10-03-1999 |
| | | | JP 2000509072 T | 18-07-2000 |
| WO 9721721 | A | 19-06-1997 | US 5707984 A | 13-01-1998 |
| | | | AT 195128 T | 15-08-2000 |
| | | | AU 1277297 A | 03-07-1997 |
| | | | CA 2239910 A | 19-06-1997 |
| | | | DE 69609632 D | 07-09-2000 |
| | | | DE 69609632 T | 09-11-2000 |
| | | | EP 0873351 A | 28-10-1998 |
| EP 0436936 | A | 17-07-1991 | DE 4000397 A | 11-07-1991 |
| | | | AU 660248 B | 15-06-1995 |
| | | | AU 6189294 A | 21-07-1994 |
| | | | AU 652928 B | 15-09-1994 |
| | | | AU 6921791 A | 05-09-1991 |
| | | | CA 2033755 A | 10-07-1991 |
| | | | HU 210905 B | 28-09-1995 |
| | | | JP 4331284 A | 19-11-1992 |
| | | | NO 910075 A | 10-07-1991 |
| | | | NZ 236709 A | 25-11-1992 |
| | | | PT 96438 A, B | 15-10-1991 |
| | | | US 5508275 A | 16-04-1996 |
| | | | US 5318987 A | 07-06-1994 |
| | | | ZA 9100132 A | 30-10-1991 |
| EP 0290885 | A | 17-11-1988 | IT 1204571 B | 10-03-1989 |
| | | | JP 63297383 A | 05-12-1988 |
| | | | US 4956384 A | 11-09-1990 |
| JP 58045724 | A | 17-03-1983 | NONE | |
| DE 19634793 | A | 05-03-1998 | NONE | |
| WO 8800202 | A | 14-01-1988 | FR 2600653 A | 31-12-1987 |
| | | | AT 88479 T | 15-05-1993 |
| | | | DE 3785505 A | 27-05-1993 |
| | | | DE 3785505 T | 28-10-1993 |
| | | | EP 0254655 A | 27-01-1988 |
| | | | JP 1500430 T | 16-02-1989 |
| | | | JP 2667418 B | 27-10-1997 |
| | | | US 4913852 A | 03-04-1990 |
| US 3702335 | A | 07-11-1972 | FR 2077750 A | 05-11-1971 |
| | | | BE 762732 A | 16-07-1971 |
| | | | CA 939335 A | 01-01-1974 |
| | | | DE 2100475 A | 02-09-1971 |
| | | | ES 387707 A | 16-05-1973 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/03238

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| US 3702335 A | | GB 1324911 A | 25-07-1973 |
| JP 4273892 A | 30-09-1992 | NONE | |